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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,029	03/16/2001	Martin C. Barnardo	1181-251	5589

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EXAMINER
COUNTS, GARY W

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
01/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/809,029	BARNARDO ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE filed 12/07/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11-17,20,22,24-27 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11-17,20,22,24-27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 7, 2007 has been entered.

Claim Rejections - 35 USC § 112

2. Claims 1-7,11-17, 2-0, 22, 24-27 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant monomeric MHC or HLA Class I molecules, does not reasonably provide enablement for recombinant MHC or HLA Class II molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of

working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method of detecting the presence of one or more allele specific anti-MHC or anti-HLA antibodies in a body fluid comprising contacting the sample with one or more immobilized recombinant MHC or HLA molecules which each bind to a different allele specific MHC or HLA antibody and detecting binding or absence of binding of the one or more allele specific antibodies to only said recombinant MHC or HLA molecules, wherein each of said one or more allele specific antibodies is specific for a particular naturally occurring MHC or HLA allele and binds to only one of said one or more recombinant MHC or HLA molecules which contains one or more epitopes of said naturally occurring MHC or HLA alleles.

The specification on page 1, lines 32-34 disclose that HLA class II molecules are coded for by the DR, DQ, DP, DO and DM regions. The specification on page 11, lines 29-37 discloses that the invention extends to class II MHC molecules. Especially preferably the MHC molecules are in monomeric form. The specification fails to provide any working examples of recombinant Class II MHC molecules. The specification provides guidance on recombinant MHC class I molecules but does not provide guidance for MHC Class II molecules and as indicated in applicants specification MHC class I and MHC class II have completely different structures and different functions (see page 1 of the specification). Further, the synthesis of class II MHC monomers at the time of the invention was not well known in the art. Barnardo et al (Transplantation, Vol 70, 531-536, No. 3, August 15, 2000) teaches that the synthesis of class II

monomer is not well known and that success of an assay would depend on successful construction of these molecules (p. 536). Thomas et al (US 6,727,070) teaches that many proteins when produced recombinantly, suffer from improper processing, folding and lack normal solubility. Frayser et al (Protein Expression and Purification 15, 105-114, 1999) teaches that recombinant complexes of class II MHC proteins with single, defined peptides or empty, peptide-free molecules have met with limited success and that they suffer from chemical and physical heterogeneity and/or low yield (p. 105). Arimilli et al (The Journal of Biological Chemistry, Vol 270, No. 2, pp. 971-977, 1995) teaches that recombinant MHC class II molecules have difficulty in folding (p. 971). Therefore, one of ordinary skill in the art would have a low level of predictability in making MHC class II monomers that present a unique epitope of a naturally occurring MHC allele and binds to anti-MHC antibodies that are specific for the naturally occurring MHC allele. At best, one of skill in the art would have to perform random experimentation to try and construct a recombinant MHC Class II monomer that would function as claimed and random experimentation is undue.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-7, 13, 16 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Barnardo et al (Detection of HLA antibodies using single recombinant HLA alleles, Human Immunology, Abstracts 1999, Volume 60, Supplement 2).

Barnardo et al., disclose a method of detecting allele specific HLA antibodies in a sample from a patient. Barnardo et al disclose biotinylated recombinant HLA molecules immobilized to a strptavidin-coated microtitre plate (7.4, p. S9). Barnardo et al disclose the recombinant molecules are biotinylated monomer preparations (HLA-A*0201 and HLA-B*0801), presenting an HIV-Gag and an HCV peptide (same monomer preparations as disclosed by applicant). Barnardo et al disclose contacting patient sera (body fluid) with the immobilized recombinant HLA molecules and detecting the binding of antibodies to the immobilized recombinant HLA molecules with detection antibodies such as anti-human IgG-HRP conjugate. Barnardo et al disclose the assay can be an ELISA assay.

It is noted that the above reference Barnardo et al has common authors which are listed as inventors in the current application. It is also noted that the above reference is considered prior art because it is considered to be by others, because the reference lists Olivia Shaw and Graham Ogg as authors and Shaw and Ogg are not listed as inventors of the current application. Therefore, it is considered to be by others.

5. Claims 1-7, 11, 13, 16 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Barnardo et al (Detection of HLA-Specific IgG using single, recombinant HLA alleles, Human Immunology (1999) Vol 60., No. Suppl. 1, pp. S1).

Barnardo et al disclose a method of detecting HLA-specific IgG using recombinant HLA molecules (p. S1). Barnardo et al disclose biotinylated recombinant HLA molecules immobilized to a strptavidin-coated microspheres. Barnardo et al also disclose that the molecules could be immobilized to ELISA plates. Barnardo et al disclose that the monomer preparation is HLA-A*0201 (same monomer preparation as disclosed by applicant). Barnardo et al disclose that antibody binding to the beads was measured by anti-human IgG-FITC conjugate.

It is noted that the above reference Barnardo et al has common authors which are listed as inventors in the current application. It is also noted that the above reference is considered prior art because it is considered to be by others, because the reference lists Graham Ogg as an author Ogg is not listed as an inventor of the current application. Therefore, it is considered to be by others.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-7 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US 5,948,627) in view Chang et al (US 5,270,169) and further in view of Walter et al (International Immunology, Vol. 9, No. 3, p.451-459, 1997).

Lee et al disclose a method for detection of HLA antibodies. Lee et al disclose adding serum from a patient to microbeads, each microbead having immobilized HLA antigens. Lee et al disclose incubating the serum and microbeads for sufficient time for anti-HLA antibodies to bind to the HLA antigens. Lee et al also disclose the addition of a labeled ligand capable of specifically binding with anti-HLA antibodies bound to the HLA antigens and detecting the presence of labeled ligand bound to the HLA antigens.

Lee et al fail to teach the use of recombinant MHC or HLA molecules.

Chang et al teaches that it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of HLA epitopes are equivalent to HLA antigens for the

detection of specific antibodies in a biological sample (col 3, lines 48-62). Chang et al teaches that the detection of the antibodies can be of antibodies to at least one HLA allele (col 2, lines 15-20). Chang et al also teaches HLA molecules can be attached to solid supports such as a microtiter plate, beads or nitrocellulose (col 3, lines 1-19).

Walter et al discloses that recombinant HLA molecules can be used to detect antibodies in a sample. Walter et al., disclose detecting a monoclonal PA2.1 antibodies (specific for HLA-A2 and A28). Walter et al disclose that this antibody binds to recombinant HLA-A2 peptide complexes. Walter et al disclose detecting the PA2.1 antibodies bound to the A2 complex with goat anti-mouse Ig conjugated to horseradish peroxidase (p. 452). Walter et al disclose that the HLA-A2 molecule is produced in E.Coli (prokaryotic expression system) (p. 451). Walter et al disclose the recombinant molecule can be immobilized and bound by antibody (p. 456, first column, lines 43 – 53). Walter et al disclose assembling the HLA-A2 (HLA-A*001) heavy chain and B_2-microglobuling in the presence of a peptide from gag protein (Gag, amino acids 77086, SLYNTVATL) (It is noted that this recombinant molecule appears to be the same recombinant molecule as disclosed by applicant (see page 23, Table 1). Walter et al disclose labeled antibodies that bind to the PA2.1 antibodies. Walter et al teaches that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes (p.456, 2nd col).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute a recombinant HLA antigen and the corresponding reagents as taught by Walter et al into the modified method of Lee et al because Chang

et al teaches that it is known in the art of detecting HLA antibodies that a synthetic HLA antigen can be substituted as an equivalent reagent for HLA antigens for the purpose of detecting HLA antibodies and Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes. Therefore, one of ordinary skill would have a reasonable expectation of success substituting recombinant HLA antigens as taught by Walter et al into the modified method of Lee et al.

10. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barnardo et al (Supplement 2) or Barnardo et al (Suppl. 1, pp. S1) in view of Pouletty et al (US 5,292,641.

See above for teachings of Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1).

Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1) differ from the instant invention in failing to teach the solid support is nitrocellulose.

Pouletty et al disclose HLA antigens which are immobilized to a nitrocellulose support (col 3, lines 22-54). Pouletty et al disclose that this immobilization of the HLA antigen provides a simple rapid and accurate method for the determination of the presence of antibodies to at least one HLA allele (col 2, lines 1-10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of a nitrocellulose support as taught by Pouletty et al into the method of Barnardo et al because Pouletty et al shows that this

immobilization provides for a simple rapid and accurate method for the determination of the presence of antibodies to at least one HLA allele.

11. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnardo et al (Supplement 2) or Barnardo et al (Suppl. 1, pp. S1)in view of Baserga et al (US 6,218,363).

See above for teachings of Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1)

Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1) is silent with respect to the recombinant HLA being synthesized in a prokaryotic expression system.

Baserga et al also disclose that MHC or HLA Class I molecules can be produced by recombinant DNA techniques. Baserga et al disclose that the recombinant MHC or HLA Class I molecule is produced in the host by expression. The transformed host may be a prokaryotic or eukaryotic cell. (col 14, lines 1-21). These recombinant molecules retain the therapeutic or diagnostic activity of the naturally occurring molecule and provides methods of identifying MHC Class I peptides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the recombinant HLA as taught by Baserga et al for the method of Barnardo et al (Supplement 2) or Barnardo et al (Suppl. 1, pp. S1) because Baserga et al shows that these recombinant molecules retain the therapeutic or diagnostic activity of the naturally occurring molecule and provides methods of identifying MHC Class I peptides.

12. Claims 20, 22, 24-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnardo et al (Detection of HLA antibodies using single recombinant HLA alleles, Human Immunology, Abstracts 1999, Volume 60, Supplement 2) or Barnardo et al (Detection of HLA-Specific IgG using single, recombinant HLA alleles, Human Immunology (1999) Vol 60., No. Suppl. 1, pp. S1) in view of Boguslaski (US 5,420,016).

See above for the teachings of Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1).

Barnardo et al (Supplement 2) and Barnardo et al (Suppl. 1, pp. S1) differ from the instant invention in failing to teach packaging the components into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various components of the method of Barnardo et al into kits such as taught by Boguslaski et al because Boguslaski shows that test kits make it more convenient and facile for the test operator.

13. Claims 20, 22, 24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al., Chang et al and Walter et al as applied to claims 1-7, 11-17 above, and further in view of Boguslaski (US 5,420,016).

See above for the teachings of Lee et al., Chang et al and Walter et al.

Lee et al., Chang et al and Walter et al differ from the instant invention in failing to teach packaging the components into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various components of the modified method of Lee et al into kits such as taught by Boguslaski et al because Boguslaski shows that test kits make it more convenient and facile for the test operator.

14. Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al., Chang et al., Walter et al and Boguslaski et al as applied to claims 1-7, 11-17, 20, 22, 24 and 29 above, and further in view of Luxembourg et al (US 2004/0137617).

See above for teachings of Lee et al., Chang et al., Walter et al and Boguslaski et al..

Lee et al., Chang et al Walter et al and Boguslaski et al differ from the instant invention in failing to teach the MHC or HLA molecule is fused to biotin.

Luxembourg et al disclose recombinant MHC molecules which are biotinylated (page 3, paragraph 0018, & page 4, paragraph 0027). Luxembourg et al disclose that these recombinant MHC molecules are biotinlyated to provide attachment to solid support coated with avidin. Luxemburg et al disclose that the use of this avidin-biotin

system provides for the isolation of peptides such as antibodies (p. 5, paragraphs 0030, and 0031).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an avidin-biotin system as taught by Luxembourg et al into the modified method of Lee et al because Luxembourg et al shows that the use of this avidin-biotin system provides for the isolation of peptides such as antibodies. Further, the use of avidin-biotin systems to immobilize and capture reagents is very well known in the art. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating avidin-biotin as taught by Luxembourg et al into the modified method of Lee et al.

Response to Arguments

15. No claims are allowed.

16. Applicant's arguments filed December 7, 2007 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art Unit 1641
December 19, 2007

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